

# Clinical Roundtable Monograph

Gastroenterology & Hepatology

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## The Management of Acute and Chronic Pancreatitis

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### Abstract

Pancreatitis, which is most generally described as any inflammation of the pancreas, is a serious condition that manifests in either acute or chronic forms. Chronic pancreatitis results from irreversible scarring of the pancreas, resulting from prolonged inflammation. Six major etiologies for chronic pancreatitis have been identified: toxic/metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, and obstruction. The most common symptom associated with chronic pancreatitis is pain localized to the upper-to-middle abdomen, along with food malabsorption, and eventual development of diabetes. Treatment strategies for acute pancreatitis include fasting and short-term intravenous feeding, fluid therapy, and pain management with narcotics for severe pain or nonsteroidal anti-inflammatories for milder cases. Patients with chronic disease and symptoms require further care to address digestive issues and the possible development of diabetes. Dietary restrictions are recommended, along with enzyme replacement and vitamin supplementation. More definitive outcomes may be achieved with surgical or endoscopic methods, depending on the role of the pancreatic ducts in the manifestation of disease.

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**Target Audience:** This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with acute and chronic pancreatitis.

**Statement of Need/Program Overview:** Acute pancreatitis usually begins with gradual or sudden pain in the upper abdomen that sometimes extends through the back. The pain is often severe and may last for several days. A patient with acute pancreatitis requires immediate medical attention. Chronic inflammation of the pancreas can lead to irreversible deterioration of the pancreatic structure and function. Chronic pancreatitis is associated with chronic abdominal pain, maldigestion, malabsorption, steatorrhea, and weight loss, and it is the most frequent cause of exocrine insufficiency. Treatment modalities are directed, when possible, at the underlying cause, and they also aim to relieve abdominal pain and symptoms related to fat malabsorption and maldigestion. Pain control is difficult in chronic pancreatitis. Narcotics have limited efficacy, and long-term treatment can induce pain tolerance and addiction. This monograph reviews the latest data on pancreatitis, including treatment approaches for pain and long-term management of chronic symptoms.

**Educational Objectives:** After completing this activity, the participant should be better able to:

1. Discuss the options for management of pain in pancreatitis.
2. Outline the safety profiles of pancreatic enzymes, narcotics, and antioxidant supplements in the treatment of pancreatitis.
3. Evaluate the efficacy of different pancreatic enzymes, including overall reduction of symptoms including pain.

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## Table of Contents

Pancreatitis Incidence and Pathophysiology Darwin L. Conwell, MD, MS	4
Management of Acute Pancreatic Symptoms Phillip P. Toskes, MD	6
Long-term Management of Patients With Chronic Pancreatitis Peter A. Banks, MD	9
Slide Library	12
CME Post-Test	15
Evaluation Form	16

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# Pancreatitis Incidence and Pathophysiology

Darwin L. Conwell, MD, MS

**P**ancreatitis, which is most generally described as any inflammation of the pancreas, is a serious condition that manifests in either acute or chronic forms. Acute pancreatitis has a sudden onset and short duration, whereas chronic pancreatitis develops gradually and worsens over time, resulting in permanent organ damage.

## Epidemiology

The incidence of acute pancreatitis varies between 4.8 to 24.2 cases per 100,000 population, according to data from England, Denmark, and the United States.<sup>1</sup> This range may be inaccurate, as many cases may be missed. Death may occur in as many as 10% of patients.<sup>2</sup> The incidence of chronic pancreatitis has not been well studied. One reason for the lack of epidemiological data has been the difficulty in achieving a generalized consensus on the classification and diagnosis of chronic pancreatitis, making it difficult to compare between studies. Most estimates are based on studies from the 1980s and 1990s performed throughout European countries.<sup>3</sup> One study in the Czech Republic showed an incidence of 7.9 cases per 100,000 persons, which was found to be relatively similar to incidence rates reported in Denmark (8.7 cases per 100,000 persons) and Germany (7.0 cases per 100,000 persons).<sup>3,4</sup> However, these rates were higher than those reported in Poland (4.0 cases per 100,000 persons) and Switzerland (1.6 cases per 100,000 persons). A more recent study in France showed a crude incidence rate between 5.86 and 7.74 cases per 100,000 persons, and a prevalence of 26.4 cases per 100,000 persons.<sup>5</sup> Differences between European countries are likely due to differences in the amount of alcohol consumed within each region.<sup>6</sup>

Some patients experience recurrent acute pancreatitis, a condition which may be difficult to distinguish from early-stage chronic pancreatitis. The incidence of recurrent acute pancreatitis is not well defined, but has been estimated to be up to 15% among patients who experienced a first acute pancreatitis attack.<sup>3</sup> One study reported an incidence of recurrent acute pancreatitis of 10.9% in patients who experienced a first attack, with 6.4% going on to develop chronic pancreatitis.<sup>7</sup>

The incidence of chronic pancreatitis is highest between 40 and 60 years of age, with a higher rate of occurrence in the male population. Differences in the occurrence of pancreatitis between males and females are likely due to dif-

ferent frequencies of various pancreatitis risk factors associated with each gender. Women have a predilection for the development of gallstones, and therefore, are more likely to develop gallstone-associated pancreatitis. Conversely, men are more likely to have alcohol-induced pancreatitis.

## Clinical Presentation

The most common symptom associated with pancreatitis is pain localized to the upper-to-middle abdomen. Patients often report that their pain radiates to the back. Acute pancreatitis is often associated with nausea or vomiting, and the pain may worsen immediately following a meal. Based on the natural history of chronic pancreatitis, Ammann and colleagues have identified 2 major types of pancreatic pain.<sup>8</sup> Type A pain is defined as having short (<10 day) episodes of acute pain separated by long pain-free periods, whereas type B pain is defined as long (1–2 month) intermittent intervals of severe pain. Type A is experienced more frequently, whereas type B pain is generally more difficult to treat. Although pain is a common symptom of patients with chronic pancreatitis, up to 20% do not experience painful episodes.

Because chronic pancreatitis results in abnormal or diminished pancreatic function, patients may also experience issues related to food malabsorption. Malabsorption is primarily related to a diminished ability to secrete enough pancreatic enzymes to properly digest fats, because pancreatic lipase is the primary pathway of fat digestion. This leads to steatorrhea, bloating, indigestion, dyspepsia, and diarrhea. Although digestion of carbohydrates and proteins may be diminished, contributions of other body systems (such as salivary amylase for the digestion of carbohydrates and gastric pepsin secretion for the digestion of proteins) limits their malabsorption.

The pancreas is a key component in the regulation of blood sugar levels, and the development of diabetes mellitus is a major complication resulting from chronic pancreatitis or severe acute necrotizing pancreatitis. Pancreatitis directly causes diabetes as a result of inflammation-induced damage to islet cells, the insulin-producing cells of the pancreas.

Acute pancreatitis inflammation can also lead to pancreatic cell death, or pancreatic necrosis. Often, this necrotized tissue becomes infected, a condition referred to as infected necrosis. Pancreatic necrosis may lead to the development

of pancreatic pseudocysts or tissue abscess, common complications associated with pancreatitis. Because pancreatic insults such as alcohol, gallstone disease, and smoking cause repeated pancreatic injury, they must be eliminated in order to reduce the extent of disease and development of permanent glandular damage.

### Pathophysiology

Together, alcohol abuse and gallstones account for over 80% of all cases of acute pancreatitis.<sup>3</sup> However, only a minority of individuals with these risk factors actually develop pancreatitis. One study calculated the estimated annual risk of developing pancreatitis was 0.05–0.2% among patients with gallstones, and further determined that small gallstones were associated with the highest risk.<sup>9</sup> Similarly, 2 studies of patients categorized as heavy drinkers suggested the risk of developing pancreatitis due to alcohol abuse was 2–3%.<sup>10,11</sup> Other causes of acute pancreatitis have also been identified. Anatomical abnormalities or pancreatic trauma may also contribute to the development of acute pancreatitis.<sup>3</sup> Examples of these structural abnormalities include pancreas divisum (a congenital defect which causes the pancreas ducts to not be properly joined), choledochal cyst (a congenital defect of the bile ducts), and obstructions (such as tumors or strictures). Metabolic disorders such as hypercalcemia and hypertriglyceridemia are also risk factors for acute pancreatitis. Other acute pancreatitis risk factors include exposure to specific medications or toxins and infection.

Chronic pancreatitis can be broadly categorized into 3 etiologies: alcohol abuse, idiopathic, and other. Alcohol abuse is the primary cause of chronic pancreatitis, accounting for approximately 70–80% of all cases.<sup>3</sup>

The TIGAR-O classification system, first proposed in 2001, identifies 6 major etiologies for chronic pancreatitis: toxic/metabolic (T), idiopathic (I), genetic (G), autoimmune (A), recurrent and severe acute pancreatitis (R), and obstruction (O).<sup>12</sup> Alcohol abuse is classified as contributing to a toxic/metabolic etiology, as are tobacco use, metabolic disorders (hypercalcemia or hyperlipidemia), and certain medications and toxins. The identification of genetic mutations as having a role in the development of chronic pancreatitis offered hope that the etiologies of pancreatitis in patients diagnosed with idiopathic disease could be determined; however, genetic alterations are not found in most of these patients.<sup>13</sup> Genetic factors are classified as autosomal dominant or autosomal recessive. Codon 29 and 122

mutations in the cationic trypsinogen gene are considered autosomal dominant, while mutations in codons 16, 22, and 23 are autosomal recessive. Other autosomal recessive mutations affect the cystic fibrosis conductance regulator (CFTR) and SPINK1 genes.

Chronic pancreatitis causes irreversible scarring of the pancreas, resulting from prolonged inflammation. The most accepted hypothesis regarding the pathogenesis of chronic pancreatitis is the sentinel acute pancreatitis event (SAPE) hypothesis, in which an initial insult or injury to the pancreas results in acute pancreatitis.<sup>14</sup> A migration of stellate cells and inflammatory reactions subsequently occurs. Repeated and prolonged pancreatic inflammation leads to the accumulation of collagen and matrix proteins. Cytokines such as tumor growth factor beta (TGFβ) cause fibrosis and scarring of the pancreatic tissue, which can result in decreased pancreatic function.

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# Management of Acute Pancreatic Symptoms

Phillip P. Toskes, MD

## Overview of Acute Pancreatitis

Acute pancreatitis is a common inflammatory condition, accounting for over 330,000 hospital admissions annually in the United States.<sup>1</sup> Early recognition of acute pancreatitis is a crucial step to allow for proper treatment and the optimal therapeutic outcome. Patients with acute pancreatitis typically present with epigastric pain that radiates to the back, and nausea and vomiting. However, these symptoms may also be characteristic of a myriad of other conditions, therefore requiring a careful assessment of the patient in order to accurately diagnose acute pancreatitis. A diagnosis of acute pancreatitis is based on the presence of 2 of the following 3 criteria: (1) characteristic abdominal pain; (2) elevated [ $\geq 3$  times the upper limit of normal (ULN)] levels of serum amylase and/or lipase; or (3) characteristic findings on a computed tomography (CT) scan.<sup>2</sup> Elevated levels of serum trypsinogen, an enzyme secreted only by the pancreas, is a valuable tool when diagnosing acute pancreatitis. Normal levels of this enzyme in patients who present with other symptoms characteristic of acute pancreatitis indicates that these symptoms are likely due to another condition.<sup>3</sup> Table 1 lists the various causes of acute pancreatitis.

In industrialized countries, the majority of acute pancreatitis cases are due to either gallstones (38%) or alcohol use (36%).<sup>4</sup> However, several other factors may be responsible for the development of acute pancreatitis, including complications following endoscopic retrograde cholangiopancreatography (ERCP), metabolic causes (such as hypertriglyceridemia or hypercalcemia), physical causes (such as a pancreatic mass), and the use of certain medications (including hydrochlorothiazide and azathioprine).<sup>4</sup> The etiology cannot be determined in approximately 20% of patients; these patients are therefore diagnosed with idiopathic acute pancreatitis.<sup>2</sup>

## Treatment Options for Acute Pancreatitis

### *Fasting and Short-term Intravenous Feeding*

Following the positive outcomes of several clinical studies, nutritional support is now considered a critical part of the treatment of patients with severe acute pancreatitis. The choice for administering nutritional support is between either enteral administration or total parenteral nutrition (TPN).<sup>5</sup> One randomized comparative study reported that hypocaloric jejunal feeding was safer and less expensive than TPN among patients with acute pancreatitis.<sup>6</sup> However, a randomized clinical study of the 2 feeding methods has not

**Table 1.** Causes of Acute Pancreatitis

Common Causes
<ul style="list-style-type: none"> <li>• Gallstones (including microlithiasis)</li> <li>• Alcohol (acute and chronic alcoholism)</li> <li>• Hypertriglyceridemia</li> <li>• Endoscopic retrograde cholangiopancreatography (ERCP), especially after biliary manometry</li> <li>• Trauma (especially blunt abdominal trauma)</li> <li>• Postoperative (abdominal and nonabdominal operations)</li> <li>• Drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications)</li> <li>• Sphincter of Oddi dysfunction</li> </ul>
Uncommon Causes
<ul style="list-style-type: none"> <li>• Vascular causes and vasculitis (ischemic-hypoperfusion states after cardiac surgery)</li> <li>• Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP)</li> <li>• Cancer of the pancreas</li> <li>• Hypercalcemia</li> <li>• Periapillary diverticulum</li> <li>• Pancreas divisum</li> <li>• Hereditary pancreatitis</li> <li>• Cystic fibrosis</li> <li>• Renal failure</li> </ul>
Rare Causes
<ul style="list-style-type: none"> <li>• Infections (mumps, coxsackievirus, cytomegalovirus, echovirus, parasites)</li> <li>• Autoimmune (eg, Sjögren's syndrome)</li> </ul>
Causes to Consider in Patients With Recurrent Bouts of Acute Pancreatitis Without an Obvious Etiology
<ul style="list-style-type: none"> <li>• Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis or sludge</li> <li>• Drugs</li> <li>• Hypertriglyceridemia</li> <li>• Pancreas divisum</li> <li>• Pancreatic cancer</li> <li>• Sphincter of Oddi dysfunction</li> <li>• Cystic fibrosis</li> <li>• Idiopathic</li> </ul>

been conducted among patients diagnosed with severe acute pancreatitis. Several studies have shown that enteral nutritional support may be successfully administered either by a gastric or jejunal route.<sup>7</sup> A randomized trial that compared



jejunal tube feeding versus oral feeding reported that while both methods were beneficial, jejunal tube feeding was associated with a lower incidence of pain,<sup>8</sup> most likely due to increased pancreatic stimulation following gastric feeding. A separate study showed that enteral feeding delivered via the mid-distal jejunum did not result in pancreatic stimulation, suggesting that this method would be preferred over the gastric route.<sup>9</sup> Administration of enteral nutrition formula via a nasogastric tube was found to be feasible and well tolerated in one study that included 26 patients with severe acute pancreatitis,<sup>10</sup> although the good results in this study have not been easy to confirm. A randomized study of 50 patients with severe acute pancreatitis showed that nasogastric feeding resulted in improved control of blood glucose levels, although these patients also experienced a higher number of complications.<sup>11</sup> Standard enteral formula is effective in this setting, and specialized formulas are unnecessary.<sup>12</sup> Recent studies comparing enteral feeding to TPN suggest that both modalities are equally efficacious and have similar side effects.<sup>13</sup>

### ***Fluid Resuscitation***

Fluid therapy has been found to play a critical role in improving the outcomes of patients with acute pancreatitis, and is a component of the supportive care recommended in the American College of Gastroenterology (ACG) Practice Guidelines.<sup>14,15</sup> Aggressive fluid resuscitation is an important treatment to counteract the hypovolemia that may accompany acute pancreatitis. Hypovolemia has a negative effect on the microcirculation within the pancreas, and can lead to further complications including hemoconcentration (hematocrit  $\geq 44$ ), tachycardia, hypotension, scant urine output, and prerenal azotemia.<sup>14</sup> Reduced volume can also result in organ failure, which is responsible for many of the early deaths attributed to acute pancreatitis. Aggressive fluid resuscitation can also be used to minimize ischemia and reperfusion injury, thereby preventing organ failure.<sup>16</sup> Although not established through clinical study, the general consensus of the amount of fluids to be administered is 250–300 cc/hour.<sup>2,17</sup> The success of fluid therapy is determined by monitoring vital signs and urine output, as well as a drop in hematocrit levels within 24 hours.<sup>14</sup>

### ***Pain Management***

Abdominal pain is one of the chief symptoms of acute pancreatitis, and can range from mild discomfort to severe pain depending on the severity of disease. Alleviation of this pain is an essential step in the management of acute pancreatitis. Parenteral narcotics are generally administered for severe acute pancreatitis.<sup>14</sup> The parenteral narcotics used in this setting include meperidine, morphine, fentanyl, and hydromorphone, among others. According to the ACG Practice Guidelines, there is no evidence to suggest the superiority of one drug over another.<sup>14</sup> The amount and fre-

quency with which these agents are administered should be closely monitored. Patient-controlled analgesia administration is used for patients who experience particularly severe pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are alternatively used as disease symptoms improve and patients are weaned off narcotic therapy.<sup>18</sup>

### ***Antibiotic Therapy***

The danger of patients with acute pancreatitis developing associated infection has led to the use of antibiotics as prophylactic therapy to prevent infected necrosis. Infection of pancreatic necrosis may develop in 40–70% of patients with severe acute pancreatitis during the second and third week after onset.<sup>19</sup> The widespread use of antibiotics in this setting is largely based on a Cochrane review of 4 randomized trials which found that prophylactic intravenous antibiotics could reduce mortality and incidence of pancreatic sepsis.<sup>20</sup> However, a subsequent meta-analysis of 7 trials, including 2 double-blind trials, concluded that prophylactic antibiotic therapy had no benefit in preventing infected necrosis or mortality.<sup>21</sup> A more recent Cochrane review showed that although the mortality rate was reduced among patients treated with prophylactic antibiotics compared with placebo (6% vs 15.3%; odds ratio, 0.37, 95% confidence interval [CI], 0.17–0.83), the rate of infected pancreatic necrosis was similar between the 2 treatment groups (20% vs 27.8%; odds ratio 0.62, 95% CI, 0.35–1.09).<sup>22</sup> In this review, the benefit associated with antibiotics was limited to beta lactam regimens, but not to quinolone or imidazole regimens. Because of the conflicting evidence regarding their use, the ACG does not recommend prophylactic antibiotic therapy for patients with pancreatic necrosis, whereas the American Gastroenterological Association guidelines recommend prophylactic antibiotics only for patients with greater than 30% necrosis of the pancreas.<sup>14,23</sup> If an infection is suspected, antibiotic therapy can be initiated and a pancreatic fine needle aspiration performed for bacteriology; treatment is then halted if an infection is not confirmed.<sup>19</sup> Otherwise, treatment should continue for 14 days.

### ***Octreotide***

Octreotide, a synthetic version of the naturally occurring peptide hormone somatostatin, has been explored as a possible treatment for acute pancreatitis. Somatostatin is a potent inhibitor of pancreatic exocrine secretion, and thus reduces or suppresses the pancreatic response to food intake.<sup>24</sup> This ability to allow the pancreas to “rest” is the primary rationale for its use in the treatment of acute pancreatitis. The half-life of somatostatin is very short (2–3 minutes), greatly limiting its therapeutic potential.<sup>25</sup> Therefore, octreotide was designed and developed to have a comparatively longer half-life (approximately 72–98 minutes).<sup>25,26</sup> However, octreotide must also be administered several times daily in order to attain therapeutic levels; thus longer-acting formulations

of octreotide requiring once-monthly administration have also been developed.<sup>27</sup> A high dose of octreotide (200 µg 3 times daily) is typically used to treat patients with severe acute pancreatitis.

A number of clinical trials have evaluated somatostatin and octreotide in patients with acute pancreatitis, and the overall conclusion from these studies is that neither agent is effective in the treatment of this disease.<sup>28,29</sup> The largest well-designed clinical trial randomized patients (n=302) with moderate to severe acute pancreatitis to receive either 1 of 2 octreotide doses (100 µg or 200 µg 3 times daily) or placebo.<sup>30</sup> However, an analysis of both the intent-to-treat and evaluable populations showed no significant difference in patient outcomes, including the mortality rate, complication rate, pain duration, need for surgical intervention, or duration of hospital stay. The study investigators concluded that octreotide had no benefit in the treatment of acute pancreatitis. More recently, a meta-analysis suggested that while octreotide and somatostatin offered no benefit in the treatment of mild acute pancreatitis, they reduced the mortality rate among patients with severe disease.<sup>31</sup> However, the majority of clinical trials included in this meta-analysis were not well designed (not randomized or controlled) and contained only a small number of study patients.<sup>29</sup> Therefore, there is currently no conclusive clinical trial evidence to support the use of either somatostatin or octreotide in the treatment of acute pancreatitis.

### Investigational Therapies

Although the pathophysiology of acute pancreatitis has not been clearly established, it is thought that reactive oxygen free radicals may play a central role. Reactive oxygen free radicals such as superoxide anions, hydrogen peroxide, and hydroxyl free radicals have been shown to be produced during a pancreatitis episode, and patients with pancreatitis have higher free radical activity.<sup>32</sup> Based on this evidence, antioxidants have been explored as a possible therapeutic agent in acute pancreatitis. Antioxidants have been shown to be partially effective in experimental models of acute pancreatitis.<sup>33,34</sup> However, to date antioxidants have only been investigated in the clinical setting to a limited extent, and require further testing in well-designed clinical trials.

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# Long-term Management of Patients With Chronic Pancreatitis

Peter A. Banks, MD

For many patients, chronic pancreatitis manifests itself as a recurring, chronic illness requiring medication to control abdominal pain and efforts to preserve quality of life. Options to treat abdominal pain include surgical and other invasive techniques. In time, some patients require pancreatic enzymes to help in digestion of food and insulin to correct diabetes mellitus.

## Small Meal Consumption and Dietary Restrictions

There is surprisingly little research focused on determining the optimal meal size for a patient with chronic pancreatitis. In the absence of clinical study, it is reasonable to suggest small meals in an attempt to decrease the secretion of pancreatic enzymes and fluids. Patients with chronic pancreatitis are advised to avoid overeating, and instead to consume smaller meals on a more frequent basis.

A low-fat diet is traditionally prescribed for patients with chronic pancreatitis to limit pancreatic enzyme secretion.<sup>1</sup> However, when discussing the low-fat diet plan with patients, physicians should keep in mind that the hormone cholecystokinin (CCK) is released in response not only to free fatty acids but also to oligopeptides and amino acids from digested food.<sup>2</sup> These facts suggest that limiting dietary protein consumption to modest amounts would also decrease pancreatic enzyme release with the goal of decreasing pancreatic pain.<sup>2</sup>

Based on increasing evidence that alcohol can cause pancreatic inflammation resulting in abdominal pain, alcohol restriction has been suggested as part of the long-term management strategy to control pancreatitis pain.<sup>3,4</sup> Complete abstinence from alcohol is unambiguously recommended for patients whose chronic pancreatitis is caused by alcohol abuse; however, it is not as clear whether patients whose disease was caused by other factors must completely abstain.

In addition to restricting alcohol, physicians should also advise their patients with chronic pancreatitis to avoid smoking.<sup>4</sup> Studies have now conclusively shown that smoking is an independent risk factor for the development of both acute and chronic pancreatitis.<sup>5,6</sup> Additionally, smoking also increases the risk of pancreatic cancer. Patients with chronic pancreatitis are already at an increased risk of developing pancreatic cancer.<sup>7,8</sup>

## Enzyme Therapy and Vitamin Supplementation

The goal of pancreatic enzyme replacement therapy for patients with steatorrhea caused by chronic pancreatitis is to achieve optimal enzyme activity in the duodenum.<sup>9</sup> This is important for patients who have lost pancreatic function either as a result of the pancreatitis itself or through surgical resection. Enzyme therapy has also been used in an effort to reduce abdominal pain associated with chronic pancreatitis.

The clinician must keep in mind several important issues when prescribing pancreatic enzymes to treat steatorrhea. First, it is important to confirm the presence of excessive fat in the stool. Traditionally, this has been done by measuring the amount of fat in a 3-day collection of stool following consumption of a prescribed diet containing a known amount (100 g) of fat. However, patients generally prefer not to participate in this method at home, and it is too expensive to keep a patient in the hospital for this purpose. Alternatively, the clinician must rely on patient self-reporting of greasy or oily stools associated with weight loss. Under these circumstances, if the use of pancreatic enzymes decreases oily stools and results in weight gain, a reasonable interpretation is that the patient did in fact have steatorrhea. A potential third method of determining that a patient has steatorrhea would be to measure fecal elastase. While a reduction in fecal elastase level indicates that there is some degree of pancreatic insufficiency, a specific level of fecal elastase has not been shown to correlate with the presence of steatorrhea.

The onset of overt steatorrhea may not occur until years after malabsorption has begun. Belated recognition of steatorrhea means that patients may have markedly delayed treatment of complications such as metabolic bone disease.

Two pancreatic enzyme preparations, pancreatin and pancrelipase, are used to reduce malabsorption and associated steatorrhea.<sup>9,10</sup> These enzymes are supplied in 2 major formulations. Pancreatic enzymes in tablet form are susceptible to inactivation by stomach acid, therefore limiting their activity in the duodenum. Strategies to circumvent this include administering higher amounts of pancreatic enzymes and increasing gastric pH with the use of a proton pump inhibitor. Alternatively, enteric-coated formulations protect pancreatic enzymes from the low pH levels present in the stomach, allowing enzymes to maintain their potency when they reach the duodenum. Enteric-coated enzymes are then released in the duodenum, where pH levels are greater than 5.5. Caplets are generally available containing 20,000 to 24,000 units of lipase. Based on the results of a randomized,

3-way crossover study, enzymes (totaling up to 96,000 units of lipase) should be administered at intervals throughout the meal in order to attain maximal results.<sup>11</sup> Although clinical studies clearly show that malabsorption and steatorrhea are improved with enzyme therapy compared to placebo, this intervention alone is not sufficient to completely abolish these steatorrhea.<sup>12</sup>

The use of pancreatic enzyme therapy to treat pancreatitis-associated pain is less certain. Enzyme preparations containing trypsin and other proteolytic enzymes are administered with the goal of decreasing cholecystokinin activity, thereby reducing pancreatic digestive enzyme secretion. However, studies testing this intervention are conflicting, and there is currently no consensus on the use of enzyme therapy to treat pancreatitis-associated abdominal pain.<sup>9,10</sup>

It is likely that most patients with chronic pancreatitis would benefit from supplementation with fat-soluble vitamins. In one study of 73 patients with chronic pancreatitis, osteopathy was found in 39% of the study population.<sup>13</sup> The authors of this study speculated that this osteopathy was due to malabsorption of vitamin D, a conclusion that has been supported by other research.<sup>14,15</sup> Therefore, patients with chronic pancreatitis should receive supplements of vitamin D (at least 1,000 units daily), should have a 25 hydroxy vitamin D level obtained at regular intervals, should receive supplemental calcium (at least 1,000 mg daily) and should be followed carefully with bone density scans at regular intervals in order to prevent the development of metabolic bone disease.

### EUS-Guided Celiac Plexus Blockade

Celiac plexus blockade (CPB) has been used for the treatment of pancreatic pain for many years.<sup>16</sup> Although its role in the control of pancreatic cancer pain is clearly established, its benefit in chronic pancreatitis pain is more controversial.<sup>17</sup> CPB is achieved through the administration of a combined injection of a corticosteroid and local anesthetic. Traditional CPB using a posterior technique may result in serious complications, including paraplegia. Therefore, endoscopic ultrasound (EUS)-guided CPB was developed to allow an anterior approach and real-time imaging of the celiac plexus. Since its inception, multiple studies have demonstrated the efficacy of EUS-guided CPB in the management of pancreatitis pain.<sup>16</sup> However, there are no well-designed randomized, prospective clinical trials evaluating EUS-guided CPB for pancreatitis pain, and there is a lack of evidence that it results in durable pain management. A review of 6 studies (n=221 patients) found that EUS-guided CPB was effective in about half (51%) of patients with chronic pancreatitis.<sup>18</sup> However, this same review concluded that although this technique was effective in this setting, there was a pressing need to improve the technique, as well as to determine those patients who would most benefit from treatment. A meta-analysis and systematic review of 8 studies (n=283 patients) concluded that EUS-guided CPB was effective in 59% of patients with chronic pancreatitis.<sup>19</sup> In patients with chronic pancreatitis,

EUS-guided CPB is generally reserved for use only after other pain management strategies have failed.<sup>20</sup> However, other reports have advocated its use early in therapy to reduce the danger of narcotic dependence.<sup>16,21</sup>

### Surgical and Endoscopic Options

Pancreatic duct dilation in some cases results from an inflammatory response occurring at the head of the pancreas blocking the duct, and in other cases for reasons that are not clear. Two randomized, prospective clinical trials have been conducted, comparing endoscopic methods with surgical techniques to alleviate pancreatitis pain.<sup>22</sup> In one, 39 patients with symptomatic chronic pancreatitis were randomized to either endoscopic or surgical treatment to drain a dilated main pancreatic duct.<sup>23</sup> During the 2-year follow-up period, patients who had received surgical treatment experienced significantly lower Izbicki pain scores (25 vs 51;  $P<.001$ ) and significantly improved physical health ( $P=.003$ ). At 2 years, more patients who had received surgical treatment achieved complete or partial pain relief compared with patients who had received endoscopic treatment (75% vs 32%;  $P=.007$ ). Additionally, patients who had received endoscopic treatment required a higher number of procedures (8 vs 3 procedures;  $P<.001$ ). In the second trial, 72 patients with painful obstructive chronic pancreatitis were randomized to either endoscopic or surgical techniques.<sup>24</sup> Although both methods were similarly successful initially, a 5-year follow-up revealed that surgery resulted in a greater durability of pain relief (34% vs 15%). Together, these clinical trials show that surgery is superior to endoscopy to achieve durable control of chronic pancreatitis pain among patients with a dilated pancreatic duct.

It is reasonable to assume that surgical procedures designed to improve drainage of the main pancreatic duct will result in decreased pain.<sup>25</sup> When the pancreatic duct becomes widely dilated (>6–7 mm), the patient becomes a candidate for surgery. The most widely used surgical technique in this setting is a lateral pancreaticojejunostomy.<sup>4</sup> Although this procedure is initially successful, resulting in short-term pain control in approximately 80% of patients, long-term follow-up studies reveal that this pain control is not durable.<sup>4</sup> Only 60% of patients experience pain relief 2 years following surgery.<sup>26,27</sup> There are several reasons that may explain why the pain relief is not durable; chief among these is the presence of other ductal obstructions not reachable during surgery.

Drainage of the pancreatic duct alone may not be sufficient to result in long-term pain relief. Approximately 30% of patients with chronic pancreatitis develop an inflammatory enlargement in the pancreatic head with a concomitant obstruction of the pancreatic duct causing diffuse dilatation of the duct.<sup>4</sup> In these cases, there are several possible surgical procedures. One is called the "Frey procedure," in which the head of the pancreas is cored out and drained with the same loop of the defunctionalized jejunum that is utilized to decompress the dilated main pancreatic duct. Another

surgical procedure is a pancreaticoduodenectomy, otherwise known as a “Whipple procedure.” This procedure results in durable pain relief in more than half of patients, but may be associated with immediate and long-term morbidity. In an attempt to avoid some of these complications, the “Beger procedure” was developed, in which the head of the pancreas is removed but the duodenum is not, and reconstruction is performed to provide drainage for the remainder of the pancreatic body and tail. Studies comparing the Whipple and Beger procedures have found that they result in similar long-term pain relief. Alternatively, a newer procedure (the “Berne procedure”) was developed for use in cases in which the head is markedly enlarged but there is no pancreatic ductal dilatation. In the Berne procedure, the head of the pancreas is cored out and drained via a defunctionalized loop of jejunum without the need for a lateral pancreaticojejunostomy. A pancreatic pseudocyst, defined as “a collection of pancreatic juice enclosed by a nonepithelialized wall that occurs as a result of acute pancreatitis, pancreatic trauma, or chronic pancreatitis,”<sup>28,29</sup> may require decompression because of abdominal pain or other symptoms. Pancreatic pseudocysts can be successfully drained and decompressed using a number of techniques. The traditional surgical technique involves gaining access through the back of the stomach; this technique can be equally effective regardless of whether the pseudocyst has adhered to the stomach or not.<sup>30</sup> Alternatively, endoscopic techniques can be used. Endoscopic treatment is largely limited by the anatomical position of the pseudocyst, but it can result in a high rate of success with relatively few complications.<sup>30</sup>

Total pancreatectomy with islet cell autotransplantation has been successfully used for the treatment of pancreatitis pain. This procedure removes the cause of pain for the patient, while restoring insulin secretory capacity and minimizing the risk of diabetes. An analysis of 188 patients who had undergone this procedure at the University of Minnesota found that over 90% of patients experienced complete pain relief and about half discontinued narcotic use. The 1-year and 10-year survival rates were 98% and 73%, respectively.<sup>31</sup> At the University of Cincinnati, an analysis of 22 patients found that 82% of patients who had required opioid analgesic therapy prior to surgery did not require it following surgery.<sup>32</sup> Endocrine function was preserved in 41% of patients. Despite these successes, several issues need to be better clarified in clinical studies in order to draw more rigorous conclusions regarding the role of this procedure in pancreatitis pain, including specifics of the patient population, the severity of disease, and the post-operative treatment course.

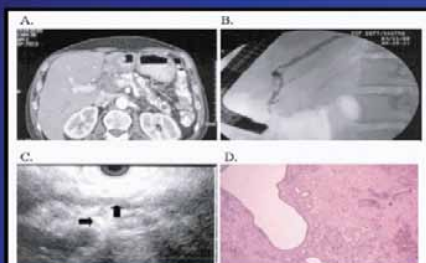
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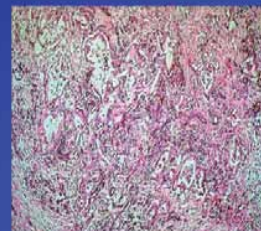
## Chronic Pancreatitis



- A. Computed tomography
- B. Endoscopic retrograde pancreatography
- C. Endoscopic ultrasound
- D. Histology

## Chronic Pancreatitis Pathology

- Gold Standard
- Patchy distribution, risk
- Features
  - Fibrosis
  - Acinar cell atrophy
  - Chronic inflammation
  - Distorted/blocked ducts
- Calcifications
  - Tropical pancreatitis
- Lymphocytic/plasma cell infiltrate
  - AIP



## CP Etiologic Classification (TIGAR-O)

- T**oxic-Metabolic
- I**diopathic
- G**enetic
- A**utoimmune
- R**ecurrent and Severe
- O**bstructive

## TIGAR-O

- **Toxic-metabolic**
  - Alcohol
  - Tobacco
  - Hypercalcemia
  - Chronic renal failure
  - Toxins
- **Idiopathic**
  - Early onset
  - Late onset
  - Tropical
- **Genetic**
  - Hereditary pancreatitis (cationic trypsinogen mutation)
  - CFTR mutations
  - SPINK 1 mutations
  - Alpha-1 antitrypsin deficiency

Adapted from: Elensad B, Whitcomb DC. Gastroenterology. 2001;120:662-707.

## TIGAR-O

- **Autoimmune**
  - Isolated autoimmune CP
  - Syndromic autoimmune CP (PSC, Sjögren's-associated, etc.)
- **Recurrent and severe AP**
  - Postnecrotic
  - Recurrent acute pancreatitis
  - Ischemic/vascular
- **Obstructive**
  - Pancreas divisum
  - Intrapapillary mucinous tumor
  - Ductal adenocarcinoma

Adapted from: Elensad B, Whitcomb DC. Gastroenterology. 2001;120:662-707.

## Chronic Pancreatitis Pathogenesis

- Early theories: Large duct/small duct
  - Alcohol injury
- Newer theories: Genetics, cell biology
- Necrosis-fibrosis concept
- Animal models
  - Superoxide dismutase, cerulein, obstruction
  - Endotoxin + alcohol = CP
- Pancreatic stellate cell
  - TGF-beta mediated fibrogenesis



**SAPE Hypothesis  
(Sentinel AP Event)**

**Step A: Acinar cell stimulation**

- Alcohol, gallstone, TG, oxidative stress

**Step B: Sentinel Event**

- Early: pro-inflammatory response
- Late: stellate cells, pro-fibrotic response

**Step C: Removal of stimulus**

- Abstinence
- Cholecystectomy
- Lipid lowering agents

**Step D: Recurrent stimulation**

- Stellate cell mediated periacinar fibrosis

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### Major Risk Factors in the Development of Severe Acute Pancreatitis

- Hypotension
- Respiratory failure
- Hypocalcemia
- Need for massive fluid and colloid replacement
- Elevated serum LDH or CRP

### Treatment of Fulminant Acute Pancreatitis

- **Hypertriglyceridemia**
  - IV amino acids
  - No fat, no carbohydrates
- **Gallstone-induced**
  - Papillotomy
- **Idiopathic**
  - Supportive Care

### Long-Term Management of Chronic Pancreatitis: Surgical and Endoscopic Options

- Lateral panceaticojejunostomy
- Whipple procedure
- Beger procedure
- Berne procedure
- Total pancreatectomy

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## Notes

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# The Management of Acute and Chronic Pancreatitis

**CME Post-Test:** *Circle the correct answer for each question below.*

- Which of the following is the most frequently encountered symptom associated with chronic pancreatitis?
  - Malabsorption
  - Abdominal pain
  - Diabetes
  - Steatorrhea
- Which of the following is NOT one of the major chronic pancreatitis etiologies included in the TIGAR-O classification system?
  - Genetic
  - Toxic/metabolic
  - Autoimmune
  - Infection
- Which of the following best describes the SAPE hypothesis?
  - A sentinel event results in acute pancreatitis, and repeated or prolonged pancreatic inflammation causes the accumulation of collagen and matrix proteins that lead to fibrosis and, ultimately, chronic pancreatitis.
  - A sentinel event results in acute pancreatitis that is quickly followed by short bouts of inflammation and, ultimately, chronic pancreatitis.
  - Repeated insults cause acute pancreatitis, which results in the accumulation of collagen and matrix proteins that lead to fibrosis and, ultimately, chronic pancreatitis.
  - A sentinel event leads directly to fibrosis, which results in the development of chronic pancreatitis.
- Which of the following is NOT one of the criteria used to diagnose acute pancreatitis?
  - Characteristic abdominal pain
  - Elevated levels of serum amylase and/or lipase
  - Characteristic findings on a CT scan
  - Low levels of serum trypsinogen
- True or False? Following the positive outcomes of several clinical studies, nutritional support is now considered a critical part of the treatment of patients with acute pancreatitis.
  - True
  - False
- Which of the following interventions is used to treat hypovolemia in patients with acute pancreatitis?
  - Short-term intravenous feeding
  - Aggressive fluid resuscitation
  - Enzyme therapy
  - EUS-guided CPB
- According to the largest well-designed clinical trial, which of the following is true regarding octreotide?
  - Octreotide had no benefit in the treatment of acute pancreatitis.
  - Octreotide reduced the mortality rate among patients with acute pancreatitis.
  - Octreotide improved the duration of pain among patients with acute pancreatitis.
  - Octreotide was only beneficial in patients with mild acute pancreatitis and was ineffective in patients with severe disease.
- According to a meta-analysis and systemic review of 8 studies including 283 patients, EUS-guided CPB was effective to treat chronic pancreatitis pain in approximately what proportion of patients?
  - 20%
  - 40%
  - 60%
  - 80%
- According to 2 randomized prospective clinical trials that compared endoscopic methods with surgical techniques to determine their ability to alleviate pancreatitis pain, which of the following is true?
  - Endoscopy is superior to surgery to achieve durable control of chronic pancreatitis pain.
  - Surgery is superior to endoscopy to achieve durable control of chronic pancreatitis pain.
  - Both endoscopy and surgery are equally effective to achieve durable control of chronic pancreatitis pain.
  - Neither endoscopy nor surgery is effective to achieve durable control of chronic pancreatitis pain.
- Based on the results of a randomized study, which of the following results in maximal efficacy of enzyme therapy?
  - A total of 96,000 units of enzyme should be administered immediately prior to beginning a meal.
  - A total of 96,000 units of enzyme should be administered immediately after completing a meal.
  - A total of 96,000 units of enzyme should be administered at intervals throughout a meal.
  - A total of 96,000 units of enzyme should be administered at intervals throughout the day.

## Evaluation Form The Management of Acute and Chronic Pancreatitis

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. *You must complete this evaluation form to receive acknowledgment for completing this activity.*

### Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

### Learning Objectives

After participating this activity, I am now better able to:

- |  |   |   |   |   |   |
|--|---|---|---|---|---|
| 1. Discuss the options for management of pain in pancreatitis.   | 1 | 2 | 3 | 4 | 5 |
| 2. Outline the safety profiles of pancreatic enzymes, narcotics, and antioxidant supplements in the treatment of pancreatitis. | 1 | 2 | 3 | 4 | 5 |
| 3. Evaluate the efficacy of different pancreatic enzymes, including overall reduction of symptoms including pain.              | 1 | 2 | 3 | 4 | 5 |

### Based upon your participation in this activity, choose the statement(s) that apply:

- ☐ I gained new strategies/skills/information that I can apply to my area of practice.  
☐ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? \_\_\_\_\_

What barriers do you see to making a change in your practice? \_\_\_\_\_

### Which of the following best describes the impact of this activity on your performance?

- ☐ I will implement the information in my area of practice.  
☐ I need more information before I can change my practice behavior.  
☐ This activity will not change my practice, as my current practice is consistent with the information presented.  
☐ This activity will not change my practice, as I do not agree with the information presented.

### Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

### The content presented:

- |   |   |   |   |   |   |
|---|---|---|---|---|---|
| Enhanced my current knowledge base              | 1 | 2 | 3 | 4 | 5 |
| Addressed my most pressing questions            | 1 | 2 | 3 | 4 | 5 |
| Promoted improvements or quality in health care | 1 | 2 | 3 | 4 | 5 |
| Was scientifically rigorous and evidence-based  | 1 | 2 | 3 | 4 | 5 |
| Avoided commercial bias or influence            | 1 | 2 | 3 | 4 | 5 |

Would you be willing to participate in a post-activity follow-up survey?   ☐ Yes   ☐ No

Please list any topics you would like to see addressed in future educational activities: \_\_\_\_\_

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

### Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

### Request for Credit

Name \_\_\_\_\_ Degree \_\_\_\_\_

Organization \_\_\_\_\_ Specialty \_\_\_\_\_

Address \_\_\_\_\_

City, State, Zip \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_

**For Physicians Only:** I certify my actual time spent to complete this educational activity to be: \_\_\_\_\_

- ☐ I participated in the entire activity and claim 1.0 credits.  
☐ I participated in only part of the activity and claim \_\_\_\_\_ credits.